REMARKS

Claims 1-13, 23-32 and 34-36 are currently pending in this application. Claims 1-6, 8, 10-13, 22-24, 27-32 and 36 are currently withdrawn from consideration. Claims 6-13, 27-32 and 36 have been amended and claim 33 has been canceled without prejudice or disclaimer in this amendment.

Claims 6-13, 27-32 and 36 have been amended in order to more particularly point out and distinctly claim the subject matter to which the applicants regard as their invention. The applicants respectfully submit that no new matter has been added. It is believed that this Amendment is fully responsive to the Office Action dated **November 17, 2003**.

Applicants election of 4-maleimidobutyryl-Ala-[Tyr(PO_3H_2)]-5-beta Ala (seq. ID. No. 18), which assertedly reads on claims 6-13 and 25-36 is acknowledged. (Office action paragraphs no. 3-5).

The Examiner states that the "elected species reads on claims 7-9, 13, 25-26 and 33-36, BUT not on" claims 6, 8, 10, 11, 13, 27-32 and 36. The Examiner therefore has additionally withdrawn claims 6, 8, 10, 11, 13, 27-32 and 36. The Examiner states that:

> "claim 6 (and claims 12, 27-32 dependent thereon) which are drawn to conjugates of a polypeptide and an analyte affinity substance do NOT **require** the presence of a maleimide and linker attached to the N-terminus." (emphasis added)

In response, Applicants respectfully note that whether the claims **require** maleimide and a

linker is not actually at issue here. What is at issue is whether the claims **read on** the elected species; that is, does the claim **encompass** the elected species. If so, the claim can be generic to the elected species.

To clarify that claims 6-13, 27-32 and 36 do read on the elected species, these withdrawn claims have been amended for clarity to change "combined product" to –reaction product–. This amended wording is supported by the description on page 25, line 18, to page 26, line 3, and on page 25, line 24, of the present specification. This amendment clarifies that the claims recite a reaction product of the polypeptide and the substance having an affinity for the analyte. For example, the amendment to claim 6 recites "a ~~combined~~ reaction product of a polypeptide ... and a substance having affinity for an analyte to be measured ..." This would include polypeptides having a maleimide group linked through an -SH group to a substance having an affinity for an analyte to be measured.

Further, claim 6 is amended to recite "a maleimide compound containing a polypeptide", to clarify that the linkage with substance (b) occurs through the maleimide group. Claim 8 is amended to be dependent on claim 6.

In withdrawn claim 10, the formula for formula (V) has been amended and labeled as formula (IV), and a new limitation, –wherein the amount of the amino acid residue having no strong acid residue can be zero–, has been added to clarify that claim 10 is generic to the elected species. This amendment is supported by the description on page 21, lines 4-15, of the specification.

Claim 11 is also amended to recite formula (IV) as discussed above. In addition, a new

limitation, –wherein the amino acid residue having no strong acid residue is present in a number of an integer of 1 to 27, while m is a integer of 3 to 30.

Accordingly, Applicants submit that newly withdrawn claims 6, 8, 10, 11, 13, 27-32 and 36, as amended, do read on the elected species. Examination of these claims is therefore respectfully requested.

Claims 7, 9, 25-26 and 33-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (Office action paragraph no. 7)

A. The Examiner states that in claim 7 (and the dependent claims), the term "strong acid residue" is not defined.

The rejection is overcome by the amendment to claim 7 incorporating the limitation of claim 33, which is correspondingly canceled. This amendment clarifies that the strong acid "is an acid having a pKa of 3 or lower".

C. (There appears to be no point (B)). The Examiner considers the terms "derived from" in claim 7 and "introducing" in claim 9 to be confusing on several points. The Examiner indicates that it is confusing as to whether claim 7 is claiming a compound or a method

Applicants respectfully disagree with the Examiner that it is unclear whether claim 7 is claiming a compound or a method. Claim 7 recites "A compound", and is clearly claiming a

compound. Since this is not a method claim, the "steps required to derive/introduce a strong acid" are not required in the claim.

With regard to the issue of the "strong acid", the rejection is overcome by the amendment to claim 7 to clarify that "strong acid" means "pKa of 3 or lower", as discussed above.

Applicants respectfully traverse the portion of the rejection regarding the terms "derived from" and "intoduced". The terminologies "derived from a strong acid" and "introduced" are used throughout the specification, and the meanings of the terms would be readily understood by one of skill in the art with reference to the specification. In particular, it is clear that this terminology refers to amino acids other than the standard 20 amino acids, and which can be viewed chemically as being amino acids derivatized to have a group from an acid considered to be a strong acid. Specific examples are the phosphorylated amino acids, considered as being derived from phosphoric acid, and the sulfated amino acids, considered as being derived from sulfuric acid.

Claims 7, 9, 26 and 33-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Kline et al. (U.S. Patent No. 5,459,078) (10/95: filed 5/91 or earlier). (Office action paragraph no. 8)

Kline et al. discloses an assay involving a capture reagent containing a first binding member conjugated to a polymeric anion substance (column 6, line 27). The Examiner refers to columns 10-16 of the reference. Column 10, line 19, indicates that the charged substance component of the capture reagent may any of a number of anionic polymers "and polyamino acids having a net

negative charge at a pH appropriate for the specific binding reaction (such as a pH in the range of 4 to 10.)" The binding member conjugated to the charged substance may be a maleimide, as seen in column 11, line 40, and disclosed in column 12, line 64, and in column 13, lines 25-29.

The Examiner states that:

> "product by process limitations (e.g. derived from a strong acids e.g. phosphoric/sulfuric) are not afforded patentable weight where the reference peptide structure is encompassed within the presently claimed structure e.g. peptides having 3 or more (strong) acid residues which encompasses asp/glu residues."

This rejection is respectfully traversed. Applicants submit that Kline et al. does not disclose polyamino acids having three or more "amino acid residues derived from a strong acid", given the meaning of this term as discussed above.

Applicants respectfully note that the Examiner has indicated that he considers Asp and Glu as strong acids. However, these are amino acids that have not been derivatized. More significantly, the pKa's of these amino acids are not "3 or less".

Applicants also note that there is no suggestion in Kline et al. for amino acids having acid groups with pKa of 3 or less. Note that page 10, lines 21-22, discuss having a net negative charge in the pH range of 4 to 10. This would not require acidic groups having a pKa of 3 or less and could be achieved with underivatized polyamino acids.

Applicants therefore submit that 7, 9, 26 and 33-35 are not anticipated by, and further are non-obvious over, Kline et al. '078. Reconsideration of the rejection is respectfully requested.

Claims 7, 9, 26 and 33-35 are rejected under 35 U.S.C. 102(e), or in the alternative obvious under 35 U.S.C. 103(a) over Foxwell et al. (U.S. Patent No. 5,459,240) (10/95: effective filing date 4/87). (Office action paragraph no. 10)

Foxwell et al. discloses a method for attaching ^{32}P to a protein based upon the introduction of a peptide region to the protein, which is capable of acting as a substrate for a phophokinase using ^{32}P-γ-ATP. The reference also discloses that the substrate molecule can be conjugated to the targeting molecule by reacting, for example, the alpha amino group with an N-hydoxysuccinimidyl ester to attach a phenyl maleimide group (column 4, lines 16-25).

The Examiner refers in particular to the substrate molecules "Foxtide I", "Foxtide II", and "Kemptide" described in column 3, lines 7-22. The Examiner cites Foxtide II in particular as having Glu, Asp and Tyr residues, noting that the Tyr sidechain is phosphorylatable.

This rejection is respectfully traversed. The example of Foxtide II has Glu, Asp and Tyr residues; however, these residues, if not phorphorylated, do **not** have pKa's of 3 or less (i.e., are not strong acids) as discussed above. There is only one serine/threonine phosphorylatable reside (i.e., Ser) in Foxtide I, Foxtide II or Kemptide. The Glu and Asp residues are not phosphorylated by the serine/threonine kinases.

Kline also discusses use of tyrosine kinases (column 3, lines 37-40). However, Foxtide I has only one tyrosine. There is no suggestion in the reference to label with both serine/threonine and tyrosine kinases simultaneously, and none of the substrate molecules in the reference has three phosphorylatable groups.

Applicants therefore submit that claims 7, 9, 26 and 33-35 are neither anticipated by nor obvious over Foxwell et al. (U.S. Patent No. 5,459,240). Reconsideration of the rejection is respectfully requested.

Claims 7, 9, 26 and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foxwell et al. (U.S. Patent No. 5,459,240) (10/95: effective filing date 4/87). (Office action paragraph no. 11)

This rejection is respectfully traversed.

The Examiner cites Ile-**Glu**-**Asp**-Asn-Glu-**Tyr**-Thr-Ala-Arg-Gln-Gly, highlighting the Glu, Asp and Tyr residues. The Examiner again appears to consider Glu, Asp and Tyr to be strong acids. However, as Applicants have discussed above, these do not have pKa's of 3 or less. Only the Tyr after phosphorylation would be a strong acid.

As noted above, there appears to be no suggestion in the reference to phosphorylate with both serine/threonine kinase and tyrosine kinase, and none of the examples in the reference appear to have three phosphorylatable residues.

Applicants therefore submit that claims 7, 9, 26 and 33-35 are not obvious over Foxwell et al. (U.S. Patent No. 5,459,240). Reconsideration of the rejection is respectfully requested.

Claims 7, 9, 26 and 33-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 (especially claims 1, 7, 8, 14, 15 and 19 of U.S. Patent No. 6,300,079). (Office action point 13)

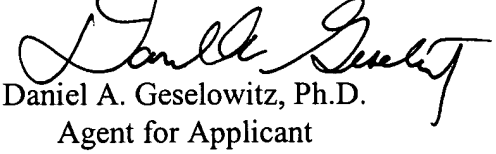
Applicants respectfully obviate the rejection under obviousness-type double patenting by the filing of a terminal disclaimer over U.S. Patent No. 6,300,079. The terminal disclaimer paper is attached.

If, for any reason, it is felt that this application is not now in condition for allowance, the Examiner is requested to contact Applicants undersigned agent at the telephone number indicated below to arrange for an interview to expedite the disposition of this case.

In the event that this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. Please charge any fees for such an extension of time and any other fees which may be due with respect to this paper, to Deposit Account No. 01-2340.

Respectfully submitted,

ARMSTRONG, KRATZ, QUINTOS, HANSON & BROOKS, LLP



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